ISSN 1070-4280, Russian Journal of Organic Chemistry, 2019, Vol. 55, No. 4, pp. 493–497. © Pleiades Publishing, Ltd., 2019.
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1-Imidoyl-1,2,3-benzotriazoles—Novel Reagents for the Synthesis of 1-Aryl-5-trifluoromethylimidazoles

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Received November 14, 2018; revised November 18, 2018; accepted December 9, 2018

Abstract—1-Imidoylbenzotriazoles [*N*-aryl-1-(1*H*-benzotriazol-1-yl)-2,2,2-trifluoroethan-1-imines] reacted with tosylmethyl isocyanide according to van Leusen's procedure to give difficultly accessible 1-aryl-4-(4-methylbenzenesulfonyl)-5-(trifluoromethyl)-1*H*-imidazoles in good yields (81–94%). The initial imidoylbenzotriazoles were conveniently synthesized by reaction of sodium benzotriazolide with the corresponding imidoyl chlorides in THF. The reactions were carried out with a wide series of imidoylbenzotriazoles containing various electron-donating and electron-withdrawing substituents in the *N*-aryl fragment.

Keywords: imidazoles, van Leusen reaction, isocyanides, trifluoromethyl-substituted azoles, benzotriazole.

DOI: 10.1134/S1070428019040122

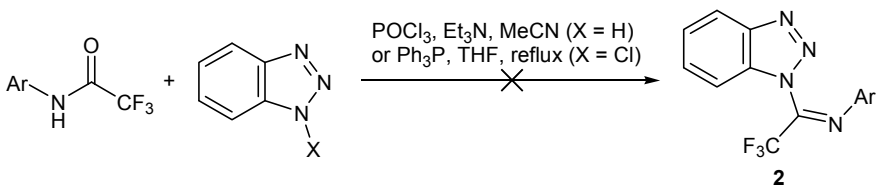
Organofluorine compounds, including fluorine-containing heterocycles, are very attractive substrates from both theoretical and practical viewpoints [1]. In recent years, fluorinated heterocycles have attracted particular attention of researchers in the field of medicinal and bioorganic chemistry. This is related to unique properties of organofluorine compounds and their very high physiological activity [2].

Introduction of fluorine atoms or fluorine-containing substituents into organic molecules often dramatically changes their chemical and pharmaceutical properties [3]. In this way, a large number of fluorine-containing drugs have been created, including antitumor agents with different mechanisms of action (fulvestrant, nilotinib, capecitabine), CNS drugs (escitalopram, rufinamide, ioflupane), and cardiovascular drugs (ezetimibe, nebivolol, prasugrel) [4–7].

We previously described a procedure for the synthesis of difficultly accessible 5-trifluoromethylimidazoles by the van Leusen reaction of imidoyl chlorides with tosylmethyl isocyanide (TosMIC) in the presence of sodium hydride [8]. This procedure, as well as classical methods [8–14] of synthesis of fluoroalkylimidazoles, made it possible to obtain 1,4,5-trisubstituted imidazoles in moderate yields.

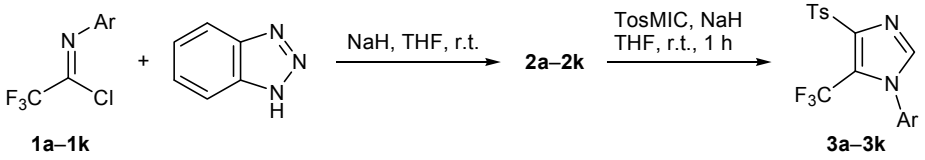
In continuation of our studies aimed at synthesizing low-molecular-weight imidazole derivatives, in this work we examined the possibility of using 1-imidoylbenzotriazoles as N^1–C^5 synthons in the synthesis of imidazoles by the van Leusen reaction with TosMIC. We tried to obtain initial imidoylbenzotriazoles **2** according to the known procedures involving treatment of substituted acetanilides with benzotriazole and phosphoryl chloride [15] or with 1-chlorobenzotriazole

Scheme 1.



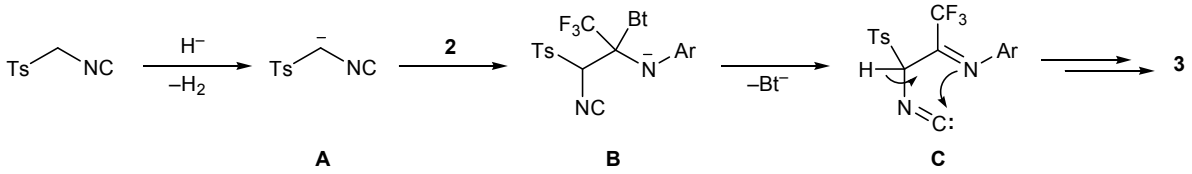
2

Scheme 2.



1–**3**, Ar = Ph (**a**), 2-MeC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 2,4-MeC_6H_3 (**d**), 4-$MeOC_6H_4$ (**e**), 4-$CF_3C_6H_4$ (**f**), 4-FC_6H_4 (**g**), 2-ClC_6H_4 (**h**), 4-ClC_6H_4 (**i**), 4-BrC_6H_4 (**j**), 4-$O_2NC_6H_4$ (**k**).

Scheme 3.



Bt = 1*H*-benzotriazol-1-yl.

and triphenylphosphine [16]. However, trifluoroacetanilides failed to react under these conditions and were recovered from the reaction mixtures (Scheme 1).

We succeeded in synthesizing required compounds **2** by direct reaction of sodium benzotriazolide with imidoyl chlorides **1a**–**1k** in THF. According to the TLC data, the reaction was complete in 1.5–2 h. Taking into account that further transformation of **2a**–**2k** is accomplished in the same solvent, we were able to obtain imidazoles **3a**–**3k** in a one-pot process by subsequent treatment of the resulting solution of **2a**–**2k** with TosMIC and sodium hydride. Imidazoles **3a**–**3k** were thus isolated in 81–94% yield (Scheme 2). The yield of **3** almost did not depend on the substituent in the *N*-aryl fragment of initial imidoylbenzotriazole **2**.

A probable reaction mechanism includes the following stages. Initially, deprotonation of TosMIC with sodium hydride generates stabilized carbanion **A** which attacks the C=N carbon atom of **2** to give intermediate adduct **B**. Elimination of benzotriazolide ion from the latter yields intermediate **C** which undergoes intramolecular cyclization leading to imidazole **3** (Scheme 3).

The ^{1}H NMR spectra of **3a**–**3k** characteristically showed a singlet of the 2-H proton of the imidazole ring at δ 8.20–8.41 ppm, as well as other signals. In the ^{19}F NMR spectra of **3a**–**3k**, fluorine atoms of the 5-trifluoromethyl group resonated in the region δ_F –53.64 to –51.81 ppm; the spectra of **3f** and **3g** contained additional singlets at δ_F –61.34 (4-$CF_3C_6H_4$) and –110.57 ppm (4-FC_6H_4), respectively.

Thus, trifluoroacetimidoylbenzotriazoles are convenient reagents for the synthesis of 5-trifluoromethyl-substituted imidazoles by reaction with tosylmethyl isocyanide. Taking into account synthetic accessibility of initial imidoyl chlorides and isocyanides, the proposed procedure makes it possible to obtain a variety of polysubstituted imidazoles containing pharmacophoric groups.

EXPERIMENTAL

The IR spectra were recorded in KBr on an FSM-1201 spectrometer. The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance 600 instrument at 600, 150, and 377 MHz, respectively using DMSO-d_6 as solvent and tetramethylsilane (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standard. The elemental compositions were determined with a Vario El Cube analyzer. The melting points were measured on a Boetius hot stage and are uncorrected.

1-Aryl-4-(4-methylbenzenesulfonyl)-5-(trifluoromethyl)-1*H*-imidazoles 3a–3k (*general procedure*). Benzotriazole, 5 mmol, was added to a suspension of 5.5 mmol of sodium hydride in 30 mL of THF. The mixture was stirred until hydrogen no longer evolved (~15 min), and a solution of imidoyl chloride **1a**–**1k** in 5 mL of THF was added dropwise. The mixture was stirred and left to stand for 1.5 h to complete the reaction (TLC, ethyl acetate–hexane, 1:9). A solution of 5 mmol of TosMIC in 10 mL of THF was added, and 5.5 mmol of sodium hydride was then added in portions over a period of 5–10 min. The mixture was stirred for 1 h and carefully treated with ice water (200 mL). The precipitate was filtered off, dried, and recrystallized from toluene–hexane (9:1).

4-(4-Methylbenzenesulfonyl)-1-phenyl-5-(trifluoromethyl)-1*H*-imidazole (3a). Yield 1.63 g (89%), beige powder, mp 201–203°C. IR spectrum, ν, cm^{-1}: 3106, 1584, 1498, 1385, 1335, 1190, 1150, 680, 593. ^1H NMR spectrum, δ, ppm: 2.42 s (3H, CH_3), 7.49 d (2H, H_{arom}, J = 8.1 Hz), 7.53–7.64 m (5H, H_{arom}), 7.87 d (2H, H_{arom}, J = 8.0 Hz), 8.28 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 21.6 (CH_3), 118.7, 120.4, 121.3, 121.5, 127.1, 128.6, 128.77, 129.9, 130.4, 130.6, 130.8, 134.9, 137.1, 142.2, 143.4, 145.5. ^{19}F NMR spectrum: δ_F –52.15 ppm. Found, %: C 55.56; H 3.67; N 7.60. $C_{17}H_{13}F_3N_2O_2S$. Calculated, %: C 55.73; H 3.58; N 7.65.

4-(4-Methylbenzenesulfonyl)-1-(2-methylphenyl)-5-(trifluoromethyl)-1*H*-imidazole (3b). Yield 1.69 g (89%), beige powder, mp 179–180°C. IR spectrum, ν, cm^{-1}: 3105, 1593, 1495, 1335, 1181, 1151, 771, 661, 594. ^1H NMR spectrum, δ, ppm: 1.97 s (3H, CH_3), 2.42 s (3H, CH_3), 7.41–7.35 m (1H, H_{arom}), 7.46 d (1H, H_{arom}, J = 7.0 Hz), 7.51 t.d (4H, H_{arom}, J = 5.5, 2.8 Hz), 7.88 d (2H, H_{arom}, J = 8.3 Hz), 8.26 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 16.8 (CH_3), 21.6 (CH_3), 127.5, 128.2, 128.6, 130.5, 131.2, 131.4, 134.0, 135.2, 137.1, 142.2, 143.3, 145.5. ^{19}F NMR spectrum: δ_F –53.47 ppm. Found, %: C 56.74; H 4.06; N 7.23. $C_{18}H_{15}F_3N_2O_2S$. Calculated, %: C 56.84; H 3.97; N 7.36.

4-(4-Methylbenzenesulfonyl)-1-(4-methylphenyl)-5-(trifluoromethyl)-1*H*-imidazole (3c). Yield 1.64 g (86%), beige powder, mp 159–161°C. IR spectrum, ν, cm^{-1}: 3104, 1594, 1516, 1472, 1337, 1191, 1152, 1006, 683, 593. ^1H NMR spectrum, δ, ppm: 2.37 s (3H, CH_3), 2.41 s (3H, CH_3), 7.36 d (2H, H_{arom}, J = 8.2 Hz), 7.45 d (2H, H_{arom}, J = 8.3 Hz), 7.48 d (2H, H_{arom}, J = 8.2 Hz); 7.88 d (2H, H_{arom}, J = 8.2 Hz), 8.24 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 21.1 (CH_3), 21.6 (CH_3), 118.7, 120.5, 121.3, 126.8, 128.0, 128.6, 129.1, 129.8, 130.3, 130.9, 132.4, 137.2, 143.4, 145.5. ^{19}F NMR spectrum: δ_F –52.25 ppm. Found, %: C 56.75; H 4.03; N 7.31. $C_{18}H_{15}F_3N_2O_2S$. Calculated, %: C 56.84; H 3.97; N 7.36.

1-(2,4-Dimethylphenyl)-4-(4-methylbenzenesulfonyl)-5-(trifluoromethyl)-1*H*-imidazole (3d). Yield 1.76 g (89%), beige powder, mp 177–179°C. IR spectrum, ν, cm^{-1}: 3111, 1596, 1336, 1261, 1185, 1154, 1008, 813, 682, 594. ^1H NMR spectrum, δ, ppm: 2.40 s (3H, CH_3), 2.42 s (3H, CH_3), 2.43 s (3H, CH_3), 7.36 s (1H, H_{arom}), 7.50 d (2H, H_{arom}, J = 8.1 Hz), 7.57–7.60 m (2H, H_{arom}), 7.88 d (2H, H_{arom}, J = 7.4 Hz), 8.29 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 19.0 (CH_3), 21.6 (CH_3), 21.6 (CH_3), 127.1, 128.7, 129.9, 130.5, 130.8, 134.9, 137.1, 142.2, 145.5. ^{19}F NMR spectrum: δ_F –53.32 ppm. Found, %: C 57.73; H 4.39; N 7.22. $C_{19}H_{17}F_3N_2O_2S$. Calculated, %: C 57.86; H 4.34; N 7.07.

1-(4-Methoxyphenyl)-4-(4-methylbenzenesulfonyl)-5-(trifluoromethyl)-1*H*-imidazole (3e). Yield 1.64 g (83%), beige powder, mp 201–202°C. IR spectrum, ν, cm^{-1}: 3110, 1586, 1502, 1336, 1261, 1185, 1154, 1008, 682, 584. ^1H NMR spectrum, δ, ppm: 2.42 s (3H, CH_3), 3.82 (3H, OCH_3), 7.07–7.11 m (2H, H_{arom}), 7.50 d.d (4H, H_{arom}, J = 8.4, 5.8 Hz), 7.86 d (2H, H_{arom}, J = 8.3 Hz), 8.20 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 21.6 (CH_3), 56.1 (OCH_3), 114.9, 121.7, 127.4, 128.5, 128.6, 130.4, 137.2, 142.3, 143.2, 145.4, 160.83. ^{19}F NMR spectrum: δ_F –52.28 ppm. Found, %: C 54.43; H 3.85; N 7.21. $C_{18}H_{15}F_3N_2O_3S$. Calculated, %: C 54.54; H 3.81; N 7.07.

4-(4-Methylbenzenesulfonyl)-5-(trifluoromethyl)-1-[4-(trifluoromethyl)phenyl]-1*H*-imidazole (3f). Yield 2.04 g (94%), brown powder, mp 149–150°C. IR spectrum, ν, cm^{-1}: 3106, 1598, 1497, 1341, 1179, 1155, 773, 666, 591. ^1H NMR spectrum, δ, ppm: 2.42 s (3H, CH_3), 7.50 d (2H, H_{arom}, J = 8.2 Hz), 7.89 d (4H, H_{arom}, J = 8.2 Hz), 7.99 d (2H, H_{arom}, J = 8.4 Hz), 8.34 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 21.6 (CH_3), 127.2, 128.4, 128.6, 130.5, 137.1, 138.4, 142.2; 143.7, 145.6. ^{19}F NMR spectrum, δ_F, ppm: –51.96 (5-CF_3), –61.34 (4′-CF_3). Found, %: C 49.66; H 2.87; N 6.50. $C_{18}H_{12}F_6N_2O_2S$. Calculated, %: C 49.77; H 2.78; N 6.45.

1-(4-Fluorophenyl)-4-(4-methylbenzenesulfonyl)-5-(trifluoromethyl)-1*H*-imidazole (3g). Yield 1.65 g (86%), beige powder, mp 164–166°C. IR spectrum, ν, cm^{-1}: 3108, 1598, 1488, 1336, 1187, 1152, 1018, 677, 596. ^1H NMR spectrum, δ, ppm: 2.42 s (3H, CH_3), 7.40–7.47 m (2H, H_{arom}), 7.50 d (2H, H_{arom}, J = 8.1 Hz), 7.67–7.74 m (2H, H_{arom}), 7.87 d (2H, H_{arom}, J = 8.3 Hz), 8.26 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 21.6 (CH_3), 116.7, 128.6, 129.7, 130.4, 131.2; 137.1, 142.3, 143.3, 145.5. ^{19}F NMR spectrum, δ_F, ppm: –52.21 (5-CF_3), –110.57 (4′-F). Found, %: C 53.01; H 3.27; N 7.22. $C_{17}H_{12}F_4N_2O_2S$. Calculated, %: C 53.13; H 3.15; N 7.29.

1-(2-Chlorophenyl)-4-(4-methylbenzenesulfonyl)-5-(trifluoromethyl)-1*H*-imidazole (3h). Yield 1.66 g (83%), beige powder, mp 198–200°C. IR spectrum, ν, cm^{-1}: 3107, 1593, 1490, 1335, 1180, 1153,

1008, 676, 594. ^{1}H NMR spectrum, δ, ppm: 2.42 s (3H, CH_3), 7.51 d (2H, H_{arom}, J = 8.1 Hz), 7.57 t.d (1H, H_{arom}, J = 7.7, 1.4 Hz), 7.66 t.d (1H, H_{arom}, J = 7.7, 1.4 Hz), 7.77 d.d (1H, H_{arom}, J = 8.1, 1.4 Hz), 7.85 d.d (1H, H_{arom}, J = 7.9, 1.6 Hz), 7.88 d (2H, H_{arom}, J = 8.3 Hz), 8.35 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 21.6 (CH_3), 118.5, 120.3, 122.1, 128.6, 128.9, 131.3, 132.5, 133.0, 137.0, 142.4, 143.3, 145.6. ^{19}F NMR spectrum: δ_F –53.64 ppm. Found, %: C 51.08; H 3.07; N 6.91. $C_{17}H_{12}ClF_3N_2O_2S$. Calculated, %: C 50.94; H 3.02; N 6.99.

1-(4-Chlorophenyl)-4-(4-methylbenzenesulfonyl)-5-(trifluoromethyl)-1*H*-imidazole (3i). Yield 1.78 g (89%), beige powder, mp 201–202°C. IR spectrum, ν, cm^{-1}: 3107, 1594, 1499, 1336, 1190, 1151, 1022, 839, 664, 593. ^{1}H NMR spectrum, δ, ppm: 2.41 s (3H, CH_3), 7.49 d (2H, H_{arom}, J = 8.1 Hz), 7.65–7.68 m (4H, H_{arom}), 7.87 d (2H, H_{arom}, J = 8.2 Hz), 8.28 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 21.6 (CH_3), 118.6, 121.4, 121.7, 128.6, 129.2, 129.3, 129.9, 130.4, 133.8, 135.6, 137.1, 142.2, 143.5, 145.5. ^{19}F NMR spectrum: δ_F –52.12 ppm. Found, %: C 50.75; H 3.09; N 6.86. $C_{17}H_{12}ClF_3N_2O_2S$. Calculated, %: C 50.94; H 3.02; N 6.99.

1-(4-Bromophenyl)-4-(4-methylbenzenesulfonyl)-5-(trifluoromethyl)-1*H*-imidazole (3j). Yield 2.05 g (92%), beige powder, mp 204–205°C. IR spectrum, ν, cm^{-1}: 3106, 1533, 1495, 1336, 1190, 1152, 1020, 836, 662, 593. ^{1}H NMR spectrum, δ, ppm: 2.41 s (3H, CH_3), 7.49 d (2H, H_{arom}, J = 8.1 Hz), 7.58 d (2H, H_{arom}, J = 8.4 Hz), 7.79 d (2H, H_{arom}, J = 8.7 Hz), 7.87 d (2H, H_{arom}, J = 8.0 Hz), 8.28 s (1H, 2-H). ^{13}C NMR spectrum, δ_C, ppm: 21.6 (CH_3), 118.6, 120.4, 121.3, 121.6, 124.2, 129.0, 130.4, 132.9, 134.2, 137.1, 142.1, 143.5, 145.5. ^{19}F NMR spectrum: δ_F –52.09 ppm. Found, %: C 45.92; H 2.81; N 6.18. $C_{17}H_{12}BrF_3N_2O_2S$. Calculated, %: C 45.86; H 2.72; N 6.29.

4-(4-Methylbenzenesulfonyl)-1-(4-nitrophenyl)-5-(trifluoromethyl)-1*H*-imidazole (3k). Yield 1.79 g (87%), brown powder, mp 265–267°C. IR spectrum, ν, cm^{-1}: 3116, 1596, 1515, 1344, 1177, 1150, 1020, 657, 592, 534. ^{1}H NMR spectrum, δ, ppm: 2.42 (3H, CH_3), 7.50 d (2H, H_{arom}, J = 8.0 Hz), 7.88 (2H, H_{arom}, J = 8.1 Hz), 7.94 d (2H, H_{arom}, J = 8.7 Hz), 8.36 s (1H, 2-H), 8.42 d (2H, H_{arom}, J = 8.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.6 (CH_3), 118.6, 120.4, 121.4, 121.7, 125.2, 128.7, 128.9, 130.5, 137.0, 140.0, 142.1, 143.8, 145.6, 148.8. ^{19}F NMR spectrum: δ_F –51.81 ppm. Found, %: C 49.55; H 3.03; N 10.08. $C_{17}H_{12}F_3N_3O_4S$. Calculated, %: C 49.64; H 2.94; N 10.22.

FUNDING

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 16-33-00349 mol_a).

CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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